II.B.1.

Like the legislative history, FDA's regulations on adequate directions for the use of drugs and devices also demonstrate that actual consumer use can be a basis for establishing a product's intended use. 21 CFR 201.5 (drugs); 21 CFR 801.5 (devices). Section 201.5, which specifies the "adequate directions" that must be provided on drug labeling, provides examples of the "intended uses" of a drug that must be included in any adequate labeling. These intended uses include both: (1) "uses for which it is prescribed, recommended, or suggested in its oral, written, print, or graphic advertising;" and (2) "*uses for which the drug is commonly used.*" 21 CFR 201.5 (emphasis added). Section 801.5 contains parallel provisions for devices. Because adequate directions for use are required only for the intended uses of a product, these regulations make the "common use" of a product a basis for determining "intended use."

Courts have also recognized that actual consumer use can be a persuasive basis for determining intent—even in the absence of other evidence that the manufacturer intends to affect the structure or function of the body. In *ASH*, the court explicitly recognized that actual "consumer intent" by itself could be a basis for imputing intent to the manufacturer:

> Clearly, it is well established "that the 'intended use' of a product, within the meaning of the Act, is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source." *Whether evidence of consumer intent is a "relevant source" for these purposes depends upon whether such evidence is strong enough to justify an inference as to the vendors' intent.* This requires a substantial showing. . . . In cases such as the one at hand, consumers must use the product predominantly—and in fact nearly exclusively—with the appropriate intent before the requisite statutory intent can be inferred.

655 F.2d at 239-240 (emphasis added). Similarly, in *NNFA v. Weinberger*, the court held that evidence before the Commissioner that vitamins "were used almost exclusively for

therapeutic purposes" could be a proper basis to determine that the manufacturer intended a pharmacological use. 512 F.2d at 703.

When a finding of an intent to affect the structure and function of the body is based exclusively on evidence of actual consumer use, the evidence must meet a high threshold. As quoted above, the courts in *ASH* and *NNFA* have indicated that the evidence should show that the actual consumer use for drug purposes is "predominant" or "nearly exclusive." FDA's regulations contemplate that the use be shown to be at least "common." 21 CFR 201.5.

There is no requirement, however, that a product be used nearly exclusively as a drug before FDA may regulate it as a drug. To the contrary, a product that has both pharmacological uses and nonpharmacological uses can be regulated as a drug. *See United States v. Guardian Chemical Corp.,* 410 F.2d 157, 162-163 (2d Cir. 1969)(a solvent used both to dissolve kidney stones (a drug use) and to clean instruments (a nondrug use) was properly regulated as a drug). Consistent with this principle, the courts recognize that where, as here, there is other evidence of manufacturer intent, consumer use for drug purposes may be relevent evidence of intended use even if that use is not predominant or nearly exclusive. *See, e.g., United States v. An Article of Device . . . Toftness Radiation Detector,* 731 F.2d 1253, 1257 (7th Cir. 1984); *United States v. 789 Cases . . . Latex Surgeons' Gloves,* 799 F. Supp. 1275, 1285, 1294-95 (D.P.R. 1992); *United States v. 22 . . . devices . . . "The Ster-o-lizer MD-200,"* 714 F. Supp. at 1165; *United States v. An Article of Device . . . "Cameron Spitler Amblo-Syntonizer,"* 261 F. Supp. 243, 245 (D. Neb. 1966).

Consistent with these authorities, the Agency finds that actual consumer use can be a basis for establishing the manufacturer's intended use for the product. Where the only evidence of intended use is the actual consumer use of the product, the Agency may need to show that the use of the product for pharmacological purposes is "predominant" or "nearly exclusive" before establishing that a product is intended to affect the structure or any function of the body. At a minimum, as set forth in FDA's regulations, the Agency should show that the use is "common" before relying exclusively on evidence of consumer use to establish intended use. Where, however, actual consumer use is only one of several types of evidence relied upon by the Agency, more limited evidence of consumer use can be used to support a finding that a product is "intended to affect the structure or any function of the body."

In the case of cigarettes and smokeless tobacco, as discussed below, the evidence establishes that the standard of "predominant" or "nearly exclusive" consumer use is met even though other types of evidence exist. Thus, the evidence of actual consumer use of cigarettes and smokeless tobacco provides an independent basis for establishing these products' intended pharmacological uses.

2. Consumers Use Cigarettes and Smokeless Tobacco for the Pharmacological Effects of Nicotine

The evidence on consumer use of cigarettes and smokeless tobacco convincingly demonstrates the intended use of such products for pharmacological purposes. In the following sections, FDA explains this conclusion and the epidemiological and experimental data that confirm that consumers *do* use cigarettes and smokeless tobacco predominantly for one or more of the pharmacological effects of nicotine.

a. Epidemiological Evidence Shows That Consumers Use Cigarettes and Smokeless Tobacco for Pharmacological Effects

Epidemiological studies establish that the vast majority of consumers use tobacco for at least one of three pharmacological purposes: to satisfy a nicotine addiction; to receive the accompanying psychoactive effects, such as relaxation and stimulation; or to control weight.

To satisfy nicotine addiction. If a tobacco consumer is addicted to nicotine, then the key reason for use of the tobacco product is a pharmacological effect: the satisfaction of the addiction.

Based upon internationally accepted definitions of addiction from the American Psychiatric Association and the World Health Organization (WHO), major recent studies show that 77% to 92% of smokers are addicted to cigarettes. In various studies, smokers who met the criteria for addiction included those identified by self-report (90% addicted),[325] those who used tobacco six or more times (87% addicted),[326] those who were daily users for at least one month (77% to 92% addicted),[327] and those who reported any current use of cigarettes (80% addicted).[328] Studies show a *higher* percentage of

[325] Hughes JR, Gust SW, Pechacek TF, Prevalence of tobacco dependence and withdrawal, *American Journal of Psychiatry* 1987;144(2):205-208. *See* AR (Vol. 81 Ref. 292).

[326] Woody GE, Cottler LB, Cacciola J, Severity of dependence: data from the DSM-IV field trials, *Addiction* 1993;88:1573-1579. *See* AR (Vol. 13 Ref. 150).

[327] Cottler L, Comparing DSM-III-R and ICD-10 substance use disorders, *Addiction* 1993;88:689-696. *See* AR (Vol. 13 Ref. 149).

[328] Hale KL, Hughes JR, Oliveto AH, Helzar JE, Higgins ST, Bickel WK, Cottler LB, Nicotine dependence in a population-based sample, in *Problems of Drug Dependence, 1992*, NIDA Research Monograph 132 (Washington DC: Government Printing Office, 1993). *See* AR (Vol. 39 Ref. 60).

addiction among tobacco users than among users of other addictive drugs, including cocaine and heroin.[329]

Although there have been no population-based studies using DSM or WHO criteria to assess rates of addiction to smokeless tobacco, substantial evidence demonstrates that a high proportion of smokeless tobacco users meet individual criteria for addiction. *See* section II.A.3.c.ii., above. This evidence strongly supports the conclusion that a substantial proportion of such users are addicted.[330] In 1992, the Inspector General of the U.S. Department of Health and Human Services estimated that approximately 75% of young regular users of smokeless tobacco are addicted.[331]

Evidence also demonstrates that many tobacco users continue to consume tobacco for an additional pharmacological reason related to addiction: to avoid withdrawal symptoms.[332] As addiction specialist Jerome Jaffe has noted, "[w]ithdrawal from nicotine . . . regularly motivates continued smoking."[333]

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[329] Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

[330] Benowitz NL, Pharmacology of smokeless tobacco use: nicotine addiction and nicotine-related health consequence, in *Smokeless Tobacco or Health*, Smoking and Tobacco Control Monograph 2 (Washington DC: Government Printing Office, 1993), at 224. *See* AR (Vol. 93 Ref. 606).

[331] Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: Government Printing Office, 1992), at 8. *See* AR (Vol. 7 Ref. 76).

[332] Hughes JR, Higgins ST, Hatsukami D, Effects of abstinence from tobacco: a critical review, *Research Advances in Alcohol and Drug Problems* 1990;10:3170398, at 381. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[333] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 529. *See* AR (Vol. 535 Ref. 96, vol. III.G).

For stimulation, sedation, mood alteration, and cognition. Studies also reveal that a large proportion of consumers use tobacco for other psychoactive effects. For example, a recent survey of young people 10 to 22 years old found that 72.8% of daily smokers and 53.8% of daily consumers of smokeless tobacco said they used tobacco for relaxation.[334] The 1988 Surgeon General's Report reviewed the epidemiological literature on the effects of smoking on mood: "The conclusion from this literature is that in the general population, persons perceive that smoking has functions that are relevant for mood regulation. Persons report that they smoke more in situations involving negative mood, and they perceive that smoking helps them to feel better in such situations."[335] The Surgeon General's Report also noted that "some cigarette smokers believe that smoking helps them to think and concentrate."[336] This is the belief of several prominent tobacco industry researchers.[337] Data demonstrating significant consumer use for the pharmacologically mediated effects of nicotine on mood and arousal are summarized in the Jurisdictional Analysis. *See* 60 FR 41579–41580.

To control weight. Numerous studies show that tobacco use by many people is at least partially motivated by their belief that tobacco will help them control their weight.

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[334] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 43 Ref. 162).

[335] Surgeon General's Report, 1988, at 399. *See* AR (Vol. 129 Ref. 1592).

[336] *Id.* at 382.

[337] Robinson J, Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 227. *See* AR (Vol. 255 Ref. 3445).

Warburton DM, Nicotine: an addictive substance or a therapeutic agent, *Progress in Drug Research* 1989;33:9-41, at 25. *See* AR (Vol. 140 Ref. 1657).

For example, in two surveys of young people, between one-third and one-half of smokers said that weight control was a reason for their smoking.[338] Additional data on the use of tobacco products for weight control are summarized in the Jurisdictional Analysis. *See* 60 FR 41580–41581.

b. Experimental Evidence Shows That Consumers Use Cigarettes and Smokeless Tobacco Products for Pharmacological Effects

As described in section II.A.3.c.i., above, overwhelming laboratory data demonstrate that nicotine's pharmacological effects are central to tobacco use. Three findings from experimental studies particularly show that consumers smoke cigarettes and consume smokeless tobacco for the pharmacological effects of nicotine.

Nicotine reinforces tobacco consumption. Like other addictive substances such as amphetamine, morphine, and cocaine, nicotine acts on a key "reward" pathway in the brain—known as the mesolimbic system—to reinforce its own consumption.[339] As even the tobacco industry has noted, the "reward" generated by this pathway may explain why people eat food, drink water, and consume salt. The ability of nicotine to generate a similar "reward" for tobacco consumption reflects its pharmacological power and represents a clear reason why consumers use tobacco products. The data supporting nicotine's role in the "reward" system are discussed in section II.A.3.c.i., above.

Nicotine controls smoking behavior. It has been convincingly demonstrated that smokers adapt their cigarette consumption to maintain the pharmacological effect of nicotine in

[338] Surgeon General's Report, 1988, at 438-441. *See* AR (Vol. 129 Ref. 1592).

[339] *See, e.g.*, Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

the brain. Thus, smokers given cigarettes lower in nicotine change their smoking behavior to obtain more nicotine, and those given cigarettes higher in nicotine than their usual brand modify their behavior to obtain less. When given a drug to reduce the effect of nicotine in the brain, smokers will consume more of the same cigarettes, even though nothing else has changed. This is compelling evidence that nicotine plays a pivotal role in why consumers use tobacco products. These data are discussed in detail in section II.A.5., above.

Nicotine in other forms affects tobacco consumers. The ability of nicotine nasal spray to produce some of the classic characteristics of addiction to nicotine supports the position that tobacco users seek tobacco primarily for the systemic pharmacological effects of nicotine. In contrast to cigarette smoke, aqueous nicotine spray does not provide any pleasing sensory characteristics. In fact, the spray can be irritating and unpleasant to use, and excessive use can cause nasal ulcerations. Notwithstanding the unpleasantness of the nicotine delivery mechanism and the presence of painful ulcerations that were further aggravated by continued use of the spray, some participants in clinical trials submitted to FDA used the spray to maintain nicotine dependence.[340]

Studies on nicotine replacement therapies also demonstrate efficacy in maintaining abstinence from smoking.[341] The ability of nicotine to promote abstinence, even when delivered through the skin, without any taste or flavor, demonstrates its key role in maintaining tobacco consumption.

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[340] FDA Drug Abuse Advisory Committee background information (Aug. 1, 1994), Joint Abuse Liability Review of Nicotine Nasal Spray. *See* AR (Vol. 9 Ref. 117).

[341] *See* appendix 1 to Jurisdictional Analysis at 62-82. *See* AR (Vol. 1 Appendix 1).

c. The Data Do Not Support the Industry's Claim That Consumers Seek Nicotine for Its Sensory Effects Rather than Its Pharmacological Effects

The tobacco industry responds to the overwhelming evidence that nicotine's pharmacological actions are central reasons for tobacco consumption by arguing instead that nicotine's key role in tobacco products is for flavor. According to the industry, the nonpharmacological actions of nicotine such as "flavor" are so essential to consumers that the nicotine level in each cigarette and unit of smokeless tobacco must be carefully controlled.

This argument in no way contradicts any of the experimental and epidemiological evidence showing that consumers use tobacco products for the pharmacological effects of nicotine. These studies prove nicotine's central pharmacological importance by demonstrating, for example, that: (1) nicotine causes psychoactive effects characteristic of addiction even when delivered by nonoral routes, where there is no "flavor" at all; and (2) the vast majority of smokers are addicted to tobacco products.

Moreover, the industry's position that nicotine's primary role is to provide flavor is inconsistent with the evidence. First, the industry's position is flatly contradicted by numerous statements of its own scientists and executives. Several industry documents dismiss the role of nicotine in flavor. For example, in 1974, an American Tobacco Company manager concluded that Pall Mall and Lucky Strike cigarettes tasted virtually the same even after the addition of extraneous nicotine (referred to as "Compound W"); according to the manager, "increasing the level of nicotine in the smoke by the addition of

Compound W has *little, if any,* effect on taste."[342] A Philip Morris presentation that discusses the importance of flavor in ultra-low cigarettes states flatly that "nicotine is an inexpensive, *tasteless* constituent."[343] Philip Morris' comments similarly contradict the industry's position that nicotine has a significant role in the flavor of cigarettes. These comments state that Philip Morris conducted extensive investigations into the flavors in cigarette smoke using an "olfactometer," yet Philip Morris claims that "[n]one of that olfactometer work involved nicotine at all," an unlikely omission if nicotine is an important flavor component.[344]

Tobacco industry documents also reveal that the industry draws a consistent distinction between nicotine's role in tobacco use and the role of flavor. A Brown & Williamson study emphasized the importance of nicotine delivery over all other product features and specifically distinguished the effects of nicotine from the taste and flavor characteristics of tobacco:

> In considering which product features are important in terms of consumer acceptance, the nicotine delivery is one of the more obvious candidates. *Others include the taste and flavour characteristics* of the smoke, physical features such as draw resistance and rate of burn, and the general uniformity of the product, to name but a few. The importance of nicotine hardly needs to be stressed, as it is so widely recognised.[345]

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[342] Memorandum from Irby RM (manager, new products division) to McCarthy JB (executive vice president, research and development), *Nicotine Content of Reconstituted Tobacco* (Jun. 5, 1974), at 3-4 (emphasis added). *See* AR (Vol. 26 Ref. 357-3)

[343] Philip Morris Inc., First Speaker, Merit Team Remarks (Jan. 14, 1976), at 3 (emphasis added). *See* AR (Vol. 640 Ref. 2).

[344] Philip Morris Inc., Comment (Apr. 19, 1996), at 47. *See* AR (Vol. 700 Ref. 226).

[345] BATCO, *Project Wheat-Part 1: Cluster profiles of U.K. male smokers and their general smoking habits,* Southampton, England (Jul. 10, 1975), at 3-4 (emphasis added). *See* AR (Vol. 20 Ref. 204-1).